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International Preliminary Examining Authority

In Re International Application of: THE GOVERNMENT OF THE UNITED STATES OF AMERICA AS REPRESENTED BY THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

International Application No.: PCT/US03/20367

International Filing Date: 26 June 2003 (26.06.03)

For: HUMANIZED ANTI-TAG 72 CC49 FOR DIAGNOSIS AND THERAPY OF HUMAN TUMORS

Date: July 21, 2004

MAIL STOP PCT, Attn: IPEA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

AMENDMENTS UNDER ARTICLE 34

Dear Officer Helms:

Submitted herewith are substitute claims under Article 34, as well as a marked-up version of the claims indicating additions and deletions. Please replace pages 56 to 63 of the international application with the attached replacement pages 56 to 63. Substitute claims 1 through 67 replace previous claims 1 through 54. Support for amended claims 1 and 23 can be found in the specification at least at page 9, lines 11-21, page 24, lines 1-16, page 40, lines 8-12, and at page 53, lines17-20. Support for amended claims 2-19, 21, 24-32, 34, 37, 39, 40, 44, 45, 47, and 50-53 can be found in the specification at least at page 40, lines 8-12. Support for amended claims 16-19 can be found in the specification at least at page 24, lines 12-16. Support for claims 55-67 can be found in the specification at least at page 22, line 20 through page 25, line 11. No new matter has been added by these amendments.

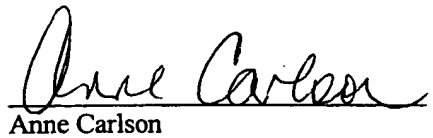
The Written Opinion alleges that original claims 1, 4-19, 21-22, 32-50, and 52 are not novel in view of WO 00/26394 (hereinafter the '394 application) because the '394 application discloses a humanized CC49 antibody having a non-conservative substitution in the light chain complementarity determining region (L-CDR) 3, a human L-CDR1, and a human L-CDR2, methods of using the humanized antibody and compositions comprising the antibody. Applicant requests reconsideration of this position, in view of the following arguments and amendments to the claims.

The substitute claims are directed to a variant humanized CC49 antibody that has both a non-conservative amino acid substitution in L-CDR3 and high binding affinity for TAG-72, compared to a parent CC49 antibody (claims 1-19, 23-31), compositions comprising the variant antibody (claims 21-22, 52), and methods of its use (claims 32-51). The '394 application discloses humanized CC49 antibodies with non-conservative substitutions in the L-CDR3, namely humanized CC49 antibodies with a tyrosine-to-threonine substitution at L-CDR3 position 94 or a leucine-to-tyrosine substitution at L-CDR3 position 96 (see the '394 application at page 29, lines 26-29, and Figure 2). However, the disclosed humanized antibodies with non-conservative substitutions at L-CDR3 positions 94 or 96 suffer a near total or total loss, respectively, in antigen binding affinity (see the '394 application at page 29, lines 5-6). Thus, the '394 application **does not** disclose humanized CC49 antibodies that have **both** a non-conservative amino acid substitution in L-CDR3 **and** high binding affinity, compared to a parent CC49 antibody. The replacement claims distinguish the invention from the alleged teachings of the '394 application. Moreover, since the '394 application discloses that non-conservative substitutions in L-CDR3 result in a loss in antigen binding affinity, this reference teaches away from making the L-CDR3 non-conservative substitution of the subject claims. Thus, the substitute claims are also inventive over the '394 application.

Applicant requests that the International Preliminary Examining Authority take into account the amended claims under Article 34 when preparing the International Preliminary Examination Report.

The Examiner is invited to telephone the undersigned at the telephone number listed below if anything further is required.

Respectfully submitted,
KLARQUIST SPARKMAN, LLP

By 
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cc: Docketing

We claim:

1. A variant humanized CC49 antibody, comprising:

a light chain complementarity determining region (L-CDR)1, a L-CDR2, and a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3,

wherein a L-CDR3 of the variant humanized CC49 antibody or of a functional fragment of the variant humanized CC49 antibody comprises a non-conservative amino acid substitution, and wherein the variant humanized CC49 antibody has a high binding affinity for TAG-72, compared to a parent CC49 antibody.

2. The variant antibody of claim 1, wherein the non-conservative substitution is a tyrosine to proline substitution.

3. The variant antibody of claim 1, wherein the non-conservative substitution is at position 91.

4. The variant antibody of claim 1, wherein the non-conservative substitution is at a position that corresponds to a ligand contact residue.

5. The variant antibody of claim 1, wherein the functional fragment is an Fab fragment, an Fv fragment, or an $F(ab')_2$ fragment.

6. The variant antibody of claim 1, wherein the L-CDR1 and L-CDR2 are a human antibody L-CDR1 and L-CDR2, respectively.

7. The variant antibody of claim 1, wherein the L-CDR3, H-CDR1, H-CDR2, and H-CDR3 are from a murine CC49 antibody.

8. The variant antibody of claim 1, wherein the high binding affinity is at least about 1.2×10^{-8} M.

9. The variant antibody of claim 8, wherein the high binding affinity is at least about 1.5×10^{-8}, about 2.0×10^{-8}, about 2.5×10^{-8}, about 3.0×10^{-8}, about 3.5×10^{-8}, about 4.0×10^{-8}, about 4.5×10^{-8}, or about 5.0×10^{-8} M.

10. The variant antibody of claim 1, wherein the antibody is minimally immunogenic.

11. The variant antibody of claim 1, wherein the antibody further comprises an effector molecule.

12. The variant antibody of claim 11, wherein the effector molecule is a detectable label.

13. The variant antibody of claim 12, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

14. The variant antibody of claim 11, wherein the effector molecule is a toxin.

15. The variant antibody of claim 14, wherein the toxin is a chemotherapeutic drug, a radioactive isotope, a bacterial toxin, a viral toxin, a cytokine or a venom protein.

16. The variant antibody of claim 1, further comprising at least one additional non-conservative amino acid substitution in the L-CDR1.

17. The variant antibody of claim 1, further comprising at least one additional non-conservative amino acid substitution in the L-CDR2, or L-CDR3.

18. The variant antibody of claim 1, further comprising at least one non-conservative amino acid substitution in the H-CDR1.

19. The antibody of claim 1, further comprising at least one non-conservative amino acid substitution in the H-CDR2, or H-CDR3.

20. A humanized CC49 antibody, wherein a nucleic acid sequence encoding the antibody has an ATCC Accession number comprising ATCC Accession number PTA-4182 or ATCC Accession number PTA-4183.

21. A nucleic acid molecule encoding the variant humanized monoclonal antibody of claim 1.

22. A vector comprising the nucleic acid of claim 21.

23. A variant humanized CC49 antibody, comprising:

a variable light framework region and a variable heavy framework region of a human antibody;

a light chain complementarity determining region (L-CDR)1, a L-CDR2, a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3, wherein at least one complementarity determining region (CDR) is a human antibody CDR and remaining CDRs are murine CC49 antibody CDRs;

a non-conservative substitution of a first residue, wherein the first residue is in the L-CDR3 of the variant antibody; and

a substitution of a second residue, wherein the second residue is in a any L-CDR or H-CDR of the variant antibody;

wherein the humanized CC49 antibody has a high binding affinity for TAG-72 and is minimally immunogenic, compared to a parent CC49 antibody.

24. The variant antibody of claim 23, wherein the non-conservative substitution of the first residue is a tyrosine to proline substitution.

25. The variant antibody of claim 23, wherein the non-conservative substitution of the first residue is at position 91.

26. The variant antibody of claim 25, wherein the non-conservative substitution of the first residue at position 91 is a tyrosine to proline substitution.

27. The variant antibody of claim 23, wherein the antibody further comprises an effector molecule.

28. The variant antibody of claim 27, wherein the effector molecule is a detectable label.

29. The variant antibody of claim 28, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

30. The variant antibody of claim 27, wherein the effector molecule is a toxin.

31. The variant antibody of claim 30, wherein the toxin is a chemotherapeutic drug, a radioactive isotope, a bacterial toxin, a viral toxin, a cytokine or a venom protein.

32. A method of detecting a TAG-72-expressing tumor in a subject, comprising:

contacting a sample obtained from the subject with the variant antibody of claim 1 for a sufficient amount of time to form an immune complex; and

detecting the presence of the immune complex, wherein the presence of the immune complex demonstrates the presence of the TAG-72-expressing tumor.

33. The method of claim 32, wherein the tumor is a colorectal tumor, a gastric tumor, a pancreatic tumor, a breast tumor, a lung tumor, an adenocarcinoma, or an ovarian tumor.

34. The method of claim 32, wherein the variant antibody further comprises an effector molecule.

35. The method of claim 34, wherein the effector molecule is a detectable label.

36. The method of claim 35, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

37. The method of claim 32, further comprising contacting the variant antibody with a secondary antibody.

38. The method of claim 37, wherein the secondary antibody further comprises a detectable label.

39. A method of detecting a TAG-72-expressing tumor in a subject, comprising:

administering the variant antibody of claim 1 to the subject for a sufficient amount of time to form an immune complex; and

detecting the presence of the immune complex, wherein the presence of the immune complex demonstrates the presence of the TAG-72-expressing tumor.

40. The method of claim 39, wherein the variant antibody further comprises an effector molecule.

41. The method of claim 40, wherein the effector molecule is a detectable label.

42. The method of claim 41, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

43. The method of claim 39, wherein the tumor is a colorectal tumor, a gastric tumor, a pancreatic tumor, a breast tumor, a lung tumor, an adenocarcinoma, or an ovarian tumor.

44. A method of treating a subject having a tumor that expresses TAG-72, comprising administering to the subject a therapeutically effective amount of the variant antibody of claim 1, wherein administering the therapeutically effective amount of the variant antibody of claim 1 inhibits the growth of the tumor or reduces the size of the tumor, thereby treating the subject.

45. The method of claim 44, wherein the administration of a therapeutically effective amount of the variant antibody of claim 1 does not elicit a human anti-murine antibody response in a subject.

46. The method of claim 44, wherein the tumor is a colorectal tumor, a gastric tumor, a pancreatic tumor, a breast tumor, a lung tumor, an adenocarcinoma, or an ovarian tumor.

47. The method of claim 44, wherein the variant antibody further comprises an effector molecule.

48. The method of claim 47, wherein the effector molecule is a toxin.

49. The method of claim 48, wherein the toxin is a chemotherapeutic drug, a radioactive isotope, a bacterial toxin, a viral toxin, a cytokine, or a venom protein.

50. The method of claim 49, wherein the variant antibody comprising a radioactive isotope is used in radioimmunotherapy.

51. A method of treating a subject having a tumor that expresses TAG-72, comprising:

administering the variant antibody of claim 1 to the subject for a sufficient amount of time to form an immune complex, wherein the variant antibody comprises a radioactive isotope;

detecting the presence of the immune complex with a hand-held gamma counter, wherein the presence of the immune complex demonstrates the presence of the TAG-72-expressing tumor; and

removing the tumor surgically, thereby treating the subject.

52. A pharmaceutical composition comprising a therapeutically effective amount of the variant antibody of claim 1 in a pharmaceutically acceptable carrier.

53. A kit, comprising a container comprising the variant antibody of claim 1.

54. The kit of claim 53, further comprising a container containing an antigen, a container containing a secondary antibody conjugated to a chemical compound, instructions for using the kit, or any combination thereof.

55. The variant antibody of claim 1, wherein the L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3 are the parent CC49 antibody L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3, respectively.

56. The variant antibody of claim 1, wherein the parent humanized CC49 antibody is HuCC49V10.

57. The variant antibody of claim 1, wherein the non-conservative substitution is a tyrosine to proline substitution at position 91.

58. The variant antibody of claim 57, further comprising a substitution of a second residue, wherein the second residue is in the L-CDR1, L-CDR2, or L-CDR3.

59. The variant antibody of claim 58, wherein the substitution of the second residue is in L-CDR1.

60. The variant antibody of claim 59, wherein the substitution of the second residue is at position 27b of the L-CDR1.

61. The variant antibody of claim 60, wherein the substitution of the second residue is a valine to leucine substitution.

62. The variant antibody of claim 23, wherein the parent CC49 antibody is HuCC49V10.

63. The variant antibody of claim 23, wherein the substitution of the second residue is in the L-CDR1, L-CDR2, or L-CDR3 of the variant antibody.

64. The variant antibody of claim 63, wherein the substitution of the second residue is in L-CDR1.

65. The variant antibody of claim 64, wherein the substitution of the second residue is at position 27b of the L-CDR1.

66. The variant antibody of claim 65, wherein the substitution of the second residue is a valine to leucine substitution.

67. The variant antibody of claim 23, wherein the non-conservative substitution of the first residue at position 91 is a tyrosine to proline substitution, the substitution of the second residue at position 27b is a valine to leucine substitution, the L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3 are the parent CC49 antibody L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3, respectively, and the parent CC49 antibody is HuCC49V10.

We claim:

1. A variant humanized CC49 antibody, comprising:

a light chain complementarity determining region (L-CDR)1, a L-CDR2, and a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3,

wherein ~~a non-conservative amino acid substitution in a light chain complementarity determining region~~ a L-CDR3 of the variant humanized CC49 antibody~~,~~ or of a functional fragment of the variant humanized CC49 antibody comprises a non-conservative amino acid substitution, and wherein the variant humanized CC49 antibody ~~that~~ has a high binding affinity for TAG-72, compared to a parent CC49 antibody.

2. The variant antibody of claim 1, wherein the non-conservative substitution is a tyrosine to proline substitution.

3. The variant antibody of claim 1, wherein the non-conservative substitution is at position 91.

4. The variant antibody of claim 1, wherein the non-conservative substitution is at a ~~residue~~ position that ~~is~~ corresponds to a ligand contact residue.

5. The variant antibody of claim 1, wherein the functional fragment is an Fab fragment, an Fv fragment, or an $F(ab')_2$ fragment.

6. The variant antibody of claim 1, wherein ~~a light chain complementarity determining region~~the L-CDR1 and ~~a light chain complementarity determining region~~ L-CDR2 are ~~from~~ a human antibody L-CDR1 and L-CDR2, respectively.

7. The variant antibody of claim 1, wherein the ~~light chain complementarity determining region~~L-CDR3, ~~a heavy chain complementarity determining region~~ H-

CDR1, ~~a heavy chain complementarity determining region~~ H-CDR2, and ~~a heavy chain complementarity determining region~~ H-CDR3 are from a murine CC49 antibody.

8. The variant antibody of claim 1, wherein the high binding affinity is at least about 1.2×10^{-8} M.

9. The variant antibody of claim 8, wherein the high binding affinity is at least about 1.5×10^{-8}, about 2.0×10^{-8}, about 2.5×10^{-8}, about 3.0×10^{-8}, about 3.5×10^{-8}, about 4.0×10^{-8}, about 4.5×10^{-8}, or about 5.0×10^{-8} M.

10. The variant antibody of claim 1, wherein the antibody is minimally immunogenic.

11. The variant antibody of claim 1, wherein the antibody further comprises an effector molecule.

12. The variant antibody of claim 11, wherein the effector molecule is a detectable label.

13. The variant antibody of claim 12, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

14. The variant antibody of claim 11, wherein the effector molecule is a toxin.

15. The variant antibody of claim 14, wherein the toxin is a chemotherapeutic drug, a radioactive isotope, a bacterial toxin, a viral toxin, a cytokine or a venom protein.

16. The variant antibody of claim 1, further comprising at least one additional non-conservative amino acid substitution in ~~a light chain complementarity determining region~~ the L-CDR1.

17. The variant antibody of claim ~~16~~1, ~~wherein the light chain complementarity determining region is a light chain complementarity determining region 1, a~~ further comprising at least one additional non-conservative amino acid substitution in the ~~light chain complementarity determining region~~ L-CDR2, or ~~a light chain complementarity determining region~~ L-CDR3.

18. The variant antibody of claim 1, further comprising at least one non-conservative amino acid substitution in ~~a heavy chain complementarity determining region~~ the H-CDR1.

19. The antibody of claim ~~18~~1, ~~wherein the heavy chain complementarity determining region is a heavy chain complementarity determining region 1, a~~ further comprising at least one non-conservative amino acid substitution in the ~~heavy chain complementarity determining region~~ H-CDR2, or ~~a heavy chain complementarity determining region~~ H-CDR3.

20. A humanized CC49 antibody, wherein a nucleic acid sequence encoding the antibody has an ATCC Accession number comprising ATCC Accession number PTA-4182 or ATCC Accession number PTA-4183.

21. A nucleic acid molecule encoding the variant humanized monoclonal antibody of claim 1.

22. A vector comprising the nucleic acid of claim 21.

23. A variant humanized CC49 antibody, comprising:

a variable light framework region and a variable heavy framework region of a human antibody;

a light chain complementarity determining region (L-CDR)1, a L-CDR2, a L-CDR3, a heavy chain complementarity determining region (H-CDR)1, a H-CDR2, and a H-CDR3, wherein at least one complementarity determining region (CDR) is ~~from the~~ a

human antibody CDR and ~~the~~ remaining ~~complementarity determining regions~~CDRs are ~~from a~~ murine CC49 antibody CDRs;

a non-conservative substitution of a first residue, wherein the first residue is in ~~a~~ the ~~light chain complementarity determining region~~ L-CDR3 of the variant antibody; and

a substitution of a second residue, wherein the second residue is in [a] any L-CDR or H-CDR ~~complementarity determining region~~ of the ~~human CC49~~ variant antibody;

wherein the humanized CC49 antibody has a high binding affinity for TAG-72 and is minimally immunogenic, compared to a parent CC49 antibody.

24. The variant antibody of claim 23, wherein the non-conservative substitution of the first residue is a tyrosine to proline substitution.

25. The variant antibody of claim 23, wherein the non-conservative substitution of the first residue is at position 91.

26. The variant antibody of claim 25, wherein the non-conservative substitution of the first residue at position 91 is a tyrosine to proline substitution.

27. The variant antibody of claim 23, wherein the antibody further comprises an effector molecule.

28. The variant antibody of claim 27, wherein the effector molecule is a detectable label.

29. The variant antibody of claim 28, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

30. The variant antibody of claim 27, wherein the effector molecule is a toxin.

31. The variant antibody of claim 30, wherein the toxin is a chemotherapeutic drug, a radioactive isotope, a bacterial toxin, a viral toxin, a cytokine or a venom protein.

32. A method of detecting a TAG-72-expressing tumor in a subject, comprising:

contacting a sample obtained from the subject with the variant antibody of claim 1 for a sufficient amount of time to form an immune complex;

detecting the presence of the immune complex, wherein the presence of the immune complex demonstrates the presence of the TAG-72-expressing tumor.

33. The method of claim 32, wherein the tumor is a colorectal tumor, a gastric tumor, a pancreatic tumor, a breast tumor, a lung tumor, an adenocarcinoma, or an ovarian tumor.

34. The method of claim 32, wherein the variant antibody further comprises an effector molecule.

35. The method of claim 34, wherein the effector molecule is a detectable label.

36. The method of claim 35, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

37. The method of claim 32, further comprising contacting the variant antibody with a secondary antibody.

38. The method of claim 37, wherein the secondary antibody further comprises a detectable label.

39. A method of detecting a TAG-72-expressing tumor in a subject, comprising:

administering the variant antibody of claim 1 to the subject for a sufficient amount of time to form an immune complex;

detecting the presence of the immune complex, wherein the presence of the immune complex demonstrates the presence of the TAG-72-expressing tumor.

40. The method of claim 39, wherein the variant antibody further comprises an effector molecule.

41. The method of claim 40, wherein the effector molecule is a detectable label.

42. The method of claim 41, wherein the detectable label comprises a radioactive isotope, an enzyme substrate, a co-factor, a ligand, a chemiluminescent agent, a fluorescent agent, a hapten, or an enzyme.

43. The method of claim 39, wherein the tumor is a colorectal tumor, a gastric tumor, a pancreatic tumor, a breast tumor, a lung tumor, an adenocarcinoma, or an ovarian tumor.

44. A method of treating a subject having a tumor that expresses TAG-72, comprising administering to the subject a therapeutically effective amount of the variant antibody of claim 1, wherein administering the therapeutically effective amount of the variant antibody of claim 1 inhibits the growth of the tumor or reduces the size of the tumor, thereby treating the subject.

45. The method of claim 44, wherein the administration of a therapeutically effective amount of the variant antibody of claim 1 does not elicit a human anti-murine antibody response in a subject.

46. The method of claim 44, wherein the tumor is a colorectal tumor, a gastric tumor, a pancreatic tumor, a breast tumor, a lung tumor, an adenocarcinoma, or an ovarian tumor.

47. The method of claim 44, wherein the variant antibody further comprises an effector molecule.

48. The method of claim 47, wherein the effector molecule is a toxin.

49. The method of claim 48, wherein the toxin is a chemotherapeutic drug, a radioactive isotope, a bacterial toxin, a viral toxin, a cytokine, or a venom protein.

50. The method of claim 49, wherein the variant antibody comprising a radioactive isotope is used in radioimmunotherapy.

51. A method of treating a subject having a tumor that expresses TAG-72, comprising:

administering the variant antibody of claim 1 to the subject for a sufficient amount of time to form an immune complex, wherein the variant antibody comprises a radioactive isotope;

detecting the presence of the immune complex with a hand-held gamma counter, wherein the presence of the immune complex demonstrates the presence of the TAG-72-expressing tumor; and

removing the tumor surgically, thereby treating the subject.

52. A pharmaceutical composition comprising a therapeutically effective amount of the variant antibody of claim 1 in a pharmaceutically acceptable carrier.

53. A kit, comprising a container comprising the variant antibody of claim 1.

54. The kit of claim 53, further comprising a container containing an antigen, a container containing a secondary antibody conjugated to a chemical compound, instructions for using the kit, or any combination thereof.

55. The variant antibody of claim 1, wherein the L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3 are the parent CC49 antibody L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3, respectively.

56. The variant antibody of claim 1, wherein the parent humanized CC49 antibody is HuCC49V10.

57. The variant antibody of claim 1, wherein the non-conservative substitution is a tyrosine to proline substitution at position 91.

58. The variant antibody of claim 57, further comprising a substitution of a second residue, wherein the second residue is in the L-CDR1, L-CDR2, or L-CDR3.

59. The variant antibody of claim 58, wherein the substitution of the second residue is in L-CDR1.

60. The variant antibody of claim 59, wherein the substitution of the second residue is at position 27b of the L-CDR1.

61. The variant antibody of claim 60, wherein the substitution of the second residue is a valine to leucine substitution.

62. The variant antibody of claim 23, wherein the parent CC49 antibody is HuCC49V10.

63. The variant antibody of claim 23, wherein the substitution of the second residue is in the L-CDR1, L-CDR2, or L-CDR3 of the variant antibody.

64. The variant antibody of claim 63, wherein the substitution of the second residue is in L-CDR1.

65. The variant antibody of claim 64, wherein the substitution of the second residue is at position 27b of the L-CDR1.

66. The variant antibody of claim 65, wherein the substitution of the second residue is a valine to leucine substitution.

67. The variant antibody of claim 23, wherein the non-conservative substitution of the first residue at position 91 is a tyrosine to proline substitution, the substitution of the second residue at position 27b is a valine to leucine substitution, the L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3 are the parent CC49 antibody L-CDR1, L-CDR2, L-CDR3, H-CDR1, H-CDR2, and H-CDR3, respectively, and the parent CC49 antibody is HuCC49V10.